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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/527,597	ANDO ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3-11, 14-16, 18-19, 21-24 and 32-33* is/are pending in the application.

4a) Of the above claim(s) *19-21 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-11, 14-16, 18, 22-23 and 32-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. Applicant's response to the Requirement for Restriction, filed on January 29, 2007 is acknowledged.

Applicant has elected the following species:

a) oligonucleotide species, a DNA oligonucleotide, as recited in Claim 6,

b) a particulate form species, solution-like, as recited in Claim 11,

c) a cell species, a mammalian cell, as recited in Claim 23, and

d) an administration route species, intra-organ, as recited in Claim 32.

Upon further examination of the subject matter, the Examiner has withdrawn the species requirement "d", drawn to administration routes.

2. Election of Applicant's invention(s) was made without traverse. Because Applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

Amendments

In the reply filed March 13, 2007, Applicant has amended Claims 1, 5-6, 11, 19 and 21, and cancelled Claims 2, 12-13, 17, 20, 25-31 and 34-35.

3. Claims 19-21 and 24 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

4. Claims 1, 3-11, 14-16, 18, 22-23 and 32-33 are under consideration.

Priority

5. This application is a 371 of PCT/JP03/11962, filed September 19, 2003. Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) regarding application JP 2002-274926, filed September 20, 2002. The certified copy of JP 2002-274926 has been filed with the instant application.

Information Disclosure Statement

6. Applicant has filed Information Disclosure Statements on March 14, 2005, June 14, 2005 and March 13, 2007. The signed and initialed PTO Forms 1449 are mailed with this action.

The information disclosure statement filed March 14, 2005 and March 13, 2007 fail to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered. The cited references "CA", "CD" and "CE" of the IDS filed March 14, 2005 and "CA", "CI" of the IDS filed March 13, 2007 are not in English and no explanation of relevance is provided to the Examiner.

The information disclosure statement filed March 13, 2007 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Specification

7. A preliminary examination of this application reveals that it includes terminology which is so different from that which is generally accepted in the art to which this invention pertains that a proper search of the prior art cannot be made. For example, the following items are not

understood: "a cross-linking degree of collagen used in the present invention is preferably a tri- or less-mer, more preferably di- or less-mer." (pg 11, lines 21-24). The term "less-mer" is not defined in the specification.

Applicant is required to provide a clarification of these matters or correlation with art-accepted terminology so that a proper comparison with the prior art can be made. Applicant should be careful not to introduce any new matter into the disclosure (i.e., matter which is not supported by the disclosure as originally filed).

A shortened statutory period for reply to this action is set to expire ONE MONTH or THIRTY DAYS, whichever is longer, from the mailing date of this letter.

Any special meaning assigned to a term "must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." *Multiform Desiccants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998). See also *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999) and MPEP § 2111.01, 2173.05(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

8. **Claims 11 and 14-16 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

With respect to Claim 11, the claim recites the term "solution-like". However, neither the claims nor the specification define the term "-like" so as to apprise the artisan the metes and bounds of the composition's state of matter. Dependent claims are included in the basis of the rejection because although they recite and encompass the composition being "solution-like", they do not clarify the nature of the term "-like".

With respect to Claim 16, the claim recites the unit limitation "by weight". However, the claimed composition is "solution-like" (dependent on Claim 11) and the solvent formulation is not recited. One of ordinary skill in the art recognizes that each solvent has its own molecular weight, and thus the mass of the collagen depends directly upon the composition of the solvent. For example, CsCl is 168.36 g/mole; whereas, NaCl is 58.442 g/mole. In the absence of the specific formulation of the solvent, the artisan cannot determine the metes and bounds of the recited wt.% range.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the Applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the Applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the Applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the Applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the Applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an

international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9. **Claims 1, 3 and 18 are rejected under 35 U.S.C. 102(b)** as being anticipated by Coester a et al (Int. J. Pharm., March 196(2): 147-149, 2000), as evidenced by Leong et al (J. Controlled Release 53(1-3):183-193, 1998).

Coester et al teach a nanoparticle complex comprising gelatin, wherein the art recognizes that gelatin is a form of collagen and is water-soluble (Leong et al, 1998), and peptide-conjugated DNA oligonucleotide.

Thus, Coester et al anticipate Claims 1, 3 and 18.

10. **Claims 1, 3 and 18 are rejected under 35 U.S.C. 102(b)** as being anticipated by Bonadio et al (U.S. Patent No. 5,763,416).

With respect to Claims 1 and 18, Bonadio et al disclose compositions for transferring a nucleic acid into bone cells or tissue (col. 3, lines 49-51), wherein the composition comprises collagen (col. 12, lines 5-12) and nucleic acid.

With respect to Claims 5-6, Bonadio et al disclose the term 'DNA segment' includes smaller fragments that one desires to transfer to a cell or tissue (col. 4, lines 1-15; col. 9, lines 40-45).

Thus, Bonadio et al anticipate Claims 1, 3 and 18.

11. **Claims 1, 3-6, 11, 14 and 18 are rejected under 35 U.S.C. 102(b)** as being anticipated by Honma et al (Biochem. and Biophys. Res. Comm., December 21, 289(5): 1075-1081, 2001), as evidenced by Friess (Eur. J. Pharm. and Biopharm. 45: 113-136, 1998).

With respect to Claims 1 and 4-5, Honma et al teach a preparation comprising atelocollagen complexed with antisense oligonucleotides, wherein the oligonucleotides were at least 20 nucleotides in length (pg 1076, col. 1, Materials and Methods).

With respect to Claims 3 and 11, Honma et al teach that atelocollagen is soluble, and may be used as a fluid or a gel (pg 1075, col. 2, ¶1), wherein the art recognizes that atelocollagen is water soluble (Friess et al, pgs 117-118, 3.3).

With respect to Claim 6, Honma et al teach the oligonucleotide to be DNA (pg 1076, col. 1, ODN).

With respect to Claim 14, Honma et al do not explicitly teach the collagen and oligonucleotide to form a 'particulate-associated body', wherein the specification discloses the term 'particulate associated body' means that a complex in which collagen with many positive charges and an oligonucleotide with negative charges are attracted electrically in a molecule, is associated with other collagen (pg 20, lines 9-12). However, Honma et al teach that atelocollagen/DNA complexes, wherein the atelocollagen is formulated at a concentration of 80μg/ml forms small particles (pg 1077, Figure 1). Thus, the atelocollagen/ODN complexes inherently possess particulate-associated bodies because, absent evidence to the contrary, only two structural components exist within the complex: atelocollagen and oligonucleotide. For such particles to be visible, the atelocollagen:oligonucleotide complex must be associated with other atelocollagen or atelocollagen:oligonucleotide complexes. Furthermore, the art has long recognized that collagen naturally forms staggered quaternary structures, e.g. helices comprising two, three or more collagen molecules (Friess, 1998).

With respect to Claim 18, the recitation of a process limitation in the claim is not viewed as positively limiting the claimed product absent a showing that the process of making recited in the claim imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the Applicants to establish a patentable distinction between the claimed and references products. The method in which the RNAs were produced is immaterial to their patentability. The structural limitations of the claim are a composition comprising a collagen and an oligonucleotide, which are fulfilled by the teachings of Honma et al.

MPEP 2113 Product-by-process Claims

PRODUCT-BY PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE

IMPLIED BY THE STEPS.

[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.).

Thus, Honma et al anticipate Claims 1, 3-6, 11, 14 and 18.

12. **Claims 1, 3-6, 11, 14-15 and 18 are rejected under 35 U.S.C. 102(b)** as being anticipated by Takei et al (J. Biol. Chem. 277(26): 23800-23806, 2002; available online April 16), as evidenced by Friess (Eur. J. Pharm. and Biopharm. 45: 113-136, 1998).

With respect to Claims 1 and 4-5, Takei et al et al teach a preparation comprising atelocollagen complexed with antisense oligonucleotides, wherein the oligonucleotides were at least 20 nucleotides in length (pg 23801, col. 1, ODNs and Liposomes; pg 23802, col. 1, first sentence; see reference cited therein for formulation details).

With respect to Claims 3 and 11, Takei et al teach that atelocollagen is soluble, and may be used as a fluid or a gel (pg 1075, col. 2, ¶1), wherein the art recognizes that atelocollagen is water soluble (Friess et al, pgs 117-118, 3.3).

With respect to Claim 6, Takei et al teach the oligonucleotide to be DNA (pg 23800, col. 2, ODN).

With respect to Claim 14, Takei et al do not explicitly teach the collagen and oligonucleotide to form a 'particulate-associated body', wherein the specification discloses the

term 'particulate associated body' means that a complex in which collagen with many positive charges and an oligonucleotide with negative charges are attracted electrically in a molecule, is associated with other collagen (pg 20, lines 9-12). However, the atelocollagen/ODN complexes inherently possess particulate-associated bodies because, absent evidence to the contrary, only two structural components exist within the complex: atelocollagen and oligonucleotide. For such particles to be visible, the atelocollagen:oligonucleotide complex must be associated with other atelocollagen or atelocollagen:oligonucleotide complexes. Furthermore, the art has long recognized that collagen naturally forms staggered quaternary structures, e.g. helices comprising two, three or more collagen molecules (Friess, 1998).

With respect to Claim 15, Takei et al does not teach the particulate to have a length of 300nm to 50μm, wherein the specification discloses the term 'long diameter' in the context the long axis of a collagen molecule (pg 20, line 15). However, at the time of the invention, the art recognized that single chain collagen fibers have a length of 300nm, and thus multimeric collagen fibers will inherently possess lengths of 300nm or more upon polymerization (Friess, 1998).

With respect to Claim 18, the recitation of a process limitation in the claim is not viewed as positively limiting the claimed product absent a showing that the process of making recited in the claim imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the Applicants to establish a patentable distinction between the claimed and references products. The method in which the RNAs were produced is immaterial to their patentability. The structural limitations of the claim are a composition comprising a collagen and an oligonucleotide, which are fulfilled by the teachings of Takei et al.

Thus, Takei et al anticipate Claims 1, 3-6, 11, 14-15 and 18.

13. **Claims 1, 3-6, 11, 14-15 and 18 are rejected under 35 U.S.C. 102(b)** as being anticipated by Takei et al (Cancer Res., December 1, 61(23): 8486-8491, 2001), as evidenced by Friess (Eur. J. Pharm. and Biopharm. 45: 113-136, 1998).

With respect to Claims 1 and 4-5, Takei et al et al teach a preparation comprising A. collagen, wherein the art recognizes the term "A. collagen" to be atelocollagen, complexed with antisense oligonucleotides, wherein the oligonucleotides were at least 20 nucleotides in length (pg 8486, col. 2, last sentence of Introduction; pg 23802, col. 1, first sentence; see reference cited therein).

With respect to Claims 3 and 11, Takei et al teach that atelocollagen is soluble, and may be used as a fluid or a gel (pg 1075, col. 2, ¶1), wherein the art recognizes that atelocollagen is water soluble (Friess et al, pgs 117-118, 3.3).

With respect to Claim 6, Takei et al teach the oligonucleotide to be DNA (pg 8486, col. 2, ODN).

With respect to Claim 14, Takei et al do not explicitly teach the collagen and oligonucleotide to form a 'particulate-associated body', wherein the specification discloses the term 'particulate associated body' means that a complex in which collagen with many positive charges and an oligonucleotide with negative charges are attracted electrically in a molecule, is associated with other collagen (pg 20, lines 9-12). However, the atelocollagen/ODN complexes inherently possess particulate-associated bodies because, absent evidence to the contrary, only two structural components exist within the complex: atelocollagen and oligonucleotide. For such particles to be visible, the atelocollagen:oligonucleotide complex must be associated with other atelocollagen or atelocollagen:oligonucleotide complexes. Furthermore, the art has long recognized that collagen naturally forms staggered quaternary structures, e.g. helices comprising two, three or more collagen molecules (Friess, 1998).

With respect to Claim 15, Takei et al does not teach the particulate to have a length of 300nm to 50μm, wherein the specification discloses the term 'long diameter' in the context the long axis of a collagen molecule (pg 20, line 15). However, at the time of the invention, the art recognized that single chain collagen fibers have a length of 300nm, and thus multimeric collagen fibers will inherently possess lengths of 300nm or more upon polymerization (Friess, 1998).

With respect to Claim 18, the recitation of a process limitation in the claim is not viewed as positively limiting the claimed product absent a showing that the process of making recited in the claim imparts a novel or unexpected property to the claimed product, as it is assumed that

equivalent products are obtainable by multiple routes. The burden is placed upon the Applicants to establish a patentable distinction between the claimed and references products. The method in which the RNAs were produced is immaterial to their patentability. The structural limitations of the claim are a composition comprising a collagen and an oligonucleotide, which are fulfilled by the teachings of Takei et al.

Thus, Takei et al anticipate Claims 1, 3-6, 11, 14-15 and 18.

14. **Claims 1, 11 and 14-16 are rejected under 35 U.S.C. 102(e)** as being anticipate by Mori et al (WO 01/34206; *of record), as evidenced by Friess (Eur. J. Pharm. and Biopharm. 45: 113-136, 1998).

With respect to Claim 1, Mori et al disclose nucleic acid-containing complex comprising a biodegradable polymer, e.g. collagen, wherein the nucleic acid may be an oligonucleotide (pg 5, lines 5-8, 15-17).

With respect to Claim 11, Mori et al disclose the polymer composition to be water-insoluble, wherein the water-insolubility property corresponds to "sparingly soluble" to "practically insoluble", and discloses a working example of a gelatin hydrogel (pg 16, lines 20-23; pg 18, lines 30-32). Because the instant specification does not define the term "solution-like", the Examiner interprets the hydrogel state of matter disclosed by Mori et al to be reasonably embraced by the instant limitation.

With respect to Claim 14, Mori et al do not explicitly teach the collagen and oligonucleotide to form a 'particulate-associated body', wherein the specification discloses the term 'particulate associated body' means that a complex in which collagen with many positive charges and an oligonucleotide with negative charges are attracted electrically in a molecule, is associated with other collagen (pg 20, lines 9-12). However, the gelatin/ODN complexes inherently possess particulate-associated bodies because, absent evidence to the contrary, only two structural components exist within the complex: gelatin (collagen) and oligonucleotide. For such particles to be visible to form a gel, the gelatin:oligonucleotide complex must be associated with other gelatin or gelatin:oligonucleotide complexes. Furthermore, the art has long recognized

that collagen naturally forms staggered quaternary structures, e.g. helices comprising two, three or more collagen molecules (Friess, 1998).

With respect to Claim 15, Mori et al does not teach the particulate to have a length of 300nm to 50μm, wherein the specification discloses the term 'long diameter' in the context the long axis of a collagen molecule (pg 20, line 15). However, at the time of the invention, the art recognized that single chain collagen fibers have a length of 300nm, and thus multimeric collagen fibers will inherently possess lengths of 300nm or more upon polymerization (Friess, 1998).

With respect to Claim 16, Mori et al disclose the hydrogel composition to comprise a water content of 99% or more (pg 18, lines 30-32), and thus the wt% of the polymer must necessarily be 1% or less.

Thus, Mori et al anticipate Claims 1, 11 and 14-16.

15. **Claims 1, 3-6, 11, 14-16 and 18 are rejected under 35 U.S.C. 102(e)** as being anticipated by Kubota et al (EP 1 295 611; *of record), as evidenced by Friess (Eur. J. Pharm. and Biopharm. 45: 113-136, 1998).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

With respect to Claims 1 and 18, Kubota et al disclose a composition comprising a collagen solution and an oligonucleotide solution (pg 6, [0017]).

With respect to Claim 3, Kubota et al disclose the collagen to be soluble in water (pg 7, [0020]).

With respect to Claim 4, Kubota et al disclose the collagen may be atelocollagen (pg 7, [0025]).

With respect to Claim 5-6, Kubota et al disclose the oligonucleotide may be DNA and may be between 5 to 30 nucleotides, wherein SEQ ID NO:1 is 20 nucleotides (pg 7; [0027-0030]).

With respect to Claims 11 and 16, Kubota et al disclose the collagen may be administered in the form of solution, wherein the collagen may present in the composition in an amount between 0.001% to 10% (pg 9, [0047]).

With respect to Claim 14, Kubota et al disclose the oligonucleotide and collagen form a particulate associated body (pg 6, [0017]).

With respect to Claim 15, Kubota et al does not teach the particulate to have a length of 300nm to 50μm, wherein the specification discloses the term 'long diameter' in the context the long axis of a collagen molecule (pg 20, line 15). However, at the time of the invention, the art recognized that single chain collagen fibers have a length of 300nm and naturally form staggered quaternary structures, e.g. helices comprising two, three or more collagen molecules (Friess, 1998). Thus, multimeric collagen fibers will inherently possess lengths of 300nm or more upon polymerization.

Thus, Kubota et al anticipate Claims 1, 3-6, 11, 14-16 and 18.

16. **Claims 1, 3-6, 14-16 and 18 are rejected under 35 U.S.C. 102(e)** as being anticipated by Kubota et al (WO 01/97857 A1; *of record), as evidenced by Friess (Eur. J. Pharm. and Biopharm. 45: 113-136, 1998).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

With respect to Claims 1 and 18, Kubota et al disclose a composition comprising a collagen and an oligonucleotide solution (pg 13). With respect to Claim 18, the recitation of a process limitation in the claim is not viewed as positively limiting the claimed product absent a

showing that the process of making recited in the claim imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the Applicants to establish a patentable distinction between the claimed and references products. The method in which the RNAs were formulated with atelocollagen is immaterial to their patentability. The structural limitations of the claim are a composition comprising a collagen and an oligonucleotide, which are fulfilled by the teachings of Kubota et al.

With respect to Claim 3, Kubota et al disclose the collagen to be soluble in water (pg 14).

With respect to Claim 4, Kubota et al disclose the collagen may be atelocollagen (pg 4).

With respect to Claim 5-6, Kubota et al disclose the oligonucleotide may be DNA and may be between 5 to 30 nucleotides, wherein SEQ ID NO:1 is 20 nucleotides (pg 4, pg 13).

With respect to Claim 14, Kubota et al disclose the oligonucleotide and collagen form a particulate associated body (pg 13).

With respect to Claim 15, Kubota et al does not teach the particulate to have a length of 300nm to 50μm, wherein the specification discloses the term 'long diameter' in the context the long axis of a collagen molecule (pg 20, line 15). However, at the time of the invention, the art recognized that single chain collagen fibers have a length of 300nm and naturally form staggered quaternary structures, e.g. helices comprising two, three or more collagen molecules (Friess, 1998). Thus, multimeric collagen fibers will inherently possess lengths of 300nm or more upon polymerization.

With respect to Claim 16, Kubota et al disclose the collagen may present in the composition in an amount of 0.5% (pgs 8-9 and 13).

Thus, Kubota et al anticipate Claims 1, 3-6, 14-16 and 18.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. **Claims 1, 3-11, 14-16, 18, 22-23 and 32-33 are rejected under 35 U.S.C. 103(a)** as being obvious over Honma et al (Biochem. and Biophys. Res. Comm., December 21, 289(5): 1075-1081, 2001) or Kubota et al (EP 1 295 611; *of record), and in further view of Kmiec (WO 97/48714; *of record).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Honma et al and Kubota et al teach atelocollagen:oligonucleotide complexes compositions to introduce oligonucleotides into cells or tissues, wherein the oligonucleotide encodes an antisense oligonucleotide to inhibit the transcription of a target mRNA.

Neither Honma et al nor Kubota et al teach a method of gene conversion using the atelocollagen:oligonucleotide composition(s). However, at the time of the invention, Kmiec disclosed oligonucleotides for the purpose of gene conversion, wherein the oligonucleotides can hybridize by Watson-Crick base pairing to a DNA having the complementary sequence, wherein the change can result in the replacement, insertion or deletion of one or more nucleotides (pg 6, lines 7-9; pg 12, Section 6.1, ¶1). Kmiec disclose that the mutator region may consist of three or fewer bases (pg 11, ¶1), wherein the art recognizes that a codon consists of three bases, and thus the insertion or deletion of one or two bases shifts the translational reading frame of the nucleic acid. Kmiec also disclosed that for a mutator region which introduces the genetic change into the target gene, the mutator region must be directly adjacent in both the 3' and 5' directions to a homology region of at least three bases, preferably between 8 and 12 bases, (pgs 9-10, joining ¶). Thus, the mutator region effecting mis-match pairing, deletion or insertion of bases is located at a central part of an oligonucleotide. Kmiec disclosed the chimeric mutational vector capable of effecting gene conversion may be used to introduce changes into the sequence of a eukaryotic gene, wherein the eukaryotic cells may be transfected with the nucleic acid using any technique known in the art for transfecting cells with DNA (pg 12, last ¶). Kmiec contemplates medical purposes to repair mutations or introduce mutations into any cell-type that can be removed from a subject's body, cultured and re-implanted into the subject (pg 13, last ¶), and teach the transfection of Chinese Hamster Ovary (CHO) cells (pg 27).

Kmiec does not teach the administration of the oligonucleotide composition to a cell in a living body; however, at the time of the invention, Kubota et al disclosed the collagen/oligonucleotide composition may be administered to a living body via diverse means, e.g. intradermic, intramuscular, transdermal, subcutaneous, intracerebral, etc... (pg 6, [0016]).

It would have been obvious to one of ordinary skill in the art to modify the oligonucleotide of Honma et al or Kubota et al to encode a nucleic acid sequence for gene

conversion as taught by Kmiec with a reasonable chance of success because the Kmiec teaches that the oligonucleotide designed for gene conversion may be formulated with any carrier known in the art for transfecting nucleic acids into cells, e.g. atelocollagen. Furthermore, there is no evidence of record disclosing that the atelocollagen is incapable of forming complexes with the gene-converting nucleic acids of Kmiec. The structural limitations of the complex, atelocollagen and nucleic acid, are independent and mutually exclusive from the intended use of the complex, e.g. antisense vs. gene conversion.

An artisan would be motivated to substitute the antisense oligonucleotide of Honma et al or Kubota et al with the gene-converting oligonucleotide of Kmiec because the gene-converting oligonucleotide will effect a molecular change in the nuclear genome of the host cell, and thus yield a permanent change in the type of gene product synthesized by the cell. In contrast, the antisense oligonucleotide will have limited therapeutic effect because the exogenous nucleic acid is impermanent and will ultimately degrade.

It also would have been obvious to one of ordinary skill in the art to substitute the means of contacting a cell with a composition comprising a gene-converting oligonucleotide as taught by Kmiec with the contacting means taught by Kubota et al with a reasonable chance of success because the art has long recognized atelocollagen to be biocompatible and demonstrate superior controlled, prolonged release of nucleic acids *in vivo*.

An artisan would be motivated to substitute *ex vivo* cell transfection with *in vivo* cell transfection because not all diseased cells are separable from the body to facilitate *ex vivo* transfection, e.g. solid tissues. Thus, an artisan may design therapies to a broader range of patient diseases than only those extant in "liquid tissues", e.g. the hematopoietic system.

Thus, the invention as a whole is *prima facie* obvious.

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER